Solution Mediated Phase Transformations Between Co-Crystals

Denise M. Croker,*[a,c] Roger J. Davey,[b] Åke C. Rasmuson[a] and Colin C. Seaton*[a]

A solution mediated transformation between two co-crystal phases has been observed for the p-toluensulfonamide/triphenylphosphine oxide co-crystal system. This system has two known co-crystals with 1:1 and 3:2 stoichiometry respectively, and the ternary phase diagram (TPD) for the system has been determined in acetonitrile previously. By manipulating the solution composition in this solvent to a region of the TPD where the 1:1 co-crystal is stable, the 3:2 co-crystal could be observed to convert to the 1:1 co-crystal. The corresponding transformation was true for the 1:1 co-crystal in a region of the TPD where the 3:2 co-crystal is stable; the 1:1 co-crystal converted to the 3:2 co-crystal.

The creation of co-crystals has recently gained increased interest within the solid-state community as a route for the modification of the physico-chemical properties of active pharmaceutical ingredients (APIs).[1-5] While the creation of such materials has been repeatedly demonstrated, studies into the crystallisation processes and transformations between such materials has only recently received attention.[6-17] However, such understanding is required to fully develop suitable crystallisation processes for the industrial synthesis of pharmaceutical co-crystals.

The key source of information for the design of a solution-based co-crystallisation is the ternary phase diagram (TPD), which indicates the thermodynamically stable phase for a given composition.[6] While previous studies have, in general, focused on the development of methodologies for the construction of TPDs and their application in the growth of a stable phase, less work has been carried out on the kinetics of the crystallisation and influence of conditions on the growth of the differing phases. The solution mediated transformation between polymorphic co-crystals has been reported for the carbamazepine/isonicotinamide system.[18] The carbamazepine/nicotinamide system has been investigated to study both the competing crystallisation kinetics of the differing phases in regions where two solid phases are stable[11] and the solution mediated transformation from carbamazepine to the co-crystal through the introduction of enough solid nicotinamide to shift the composition into a different region of the TPD.[14] In the carbamazepine/nicotinamide system only a single co-crystal phase is known and so only the conversion between the starting materials and the co-crystal are possible. While a number of systems exhibit co-crystals of differing stoichiometry and the identification of the regions of the TPD where the differing phases are stable has been reported,[16,19,20] the conversion process between these differing co-crystal phases has not been fully investigated.

It has been shown for some co-crystal systems that the relative stability of co-crystals with differing stoichiometries can be altered through the choice of solvent. For example, the benzoic acid/isonicotinamide pair has two co-crystals: one with a 1:1 composition and one with a 2:1 composition.[21] Both phases have been shown to be stable in different aqueous solution compositions but only the 1:1 co-crystal is stable in ethanolic solutions. This was demonstrated by the addition of crystals of the 2:1 phase to a saturated solution, which lead to the complete dissolution of the 2:1 crystals in 20 minutes, followed by crystallisation of the 1:1 phase after 10 hours.[13] Understanding the balance of stability between the differing phases and the choice of solvent is thus required to design suitable conditions for the controlled growth of selected phases. Such understanding was recently applied to the successful growth of crystals suitable for single crystal structure determination of the 1:2 malic acid and caffeine co-crystal. This malic acid/caffeine system exists in two stoichiometries (1:1 and 1:2) and both phases are readily obtainable through solid-state grinding. However, only crystals of the 1:1 phase suitable for single crystal structure solution could be obtained by slow evaporation of dichloromethane solution.[5] In contrast, only poorly diffracting crystals of the 1:2 co-crystal could be produced through anti-solvent addition of cyclohexane to a saturated 1:2 solution in 15:1 chloroform/methanol mixture. Investigations into the relative solubilities of the components indicated significant differences between the two components for the majority of solvents and construction of the ternary phase diagram for malic acid/caffeine/acetone indicated that the 1:2 system was metastable for this system.[20] Selection of a solvent that reduced the differences in solubility lead to the identification of a system where both co-crystal phase were stable. Construction of the TPD for malic acid/caffeine/ethyl acetate allowed for the controlled growth of the 1:2 co-crystal.[22]

For polymorphic systems, solution mediated transformations are an important process for the conversion of metastable phases into stable crystalline phases.[23,24] While the general mechanism is the dissolution of the metastable phase and regrowth of the stable one, these conversions may also occur through heterogeneous nucleation driven by an epitaxial interaction between the two phases due to similarities in selected surfaces of the two forms.[24] For example, the solution mediated transformation of α to β glutamic acid occurs by nucleation of the β phase on the {111} faces of the α phase.[25-28] Recently, work in identifying the different possible transformation scenarios for polymorph transformations has highlighted the balance between dissolution of the metastable phase and the nucleation and growth of the stable phase.[29] Similar factors will control the transformation of metastable co-crystal phases to stable co-crystal phases, however unlike polymorphic systems the stability of a given co-crystal is dependant on the composition of the solution. Thus the transformation process can be easily studied by the addition of crystals of one co-crystal into a solution with a composition where the other co-crystal is stable.

The system comprising *p*-toulenesulfonamide (TSA) and triphenylphosphine oxide (PH_3PO) was initially reported to form as a 3:2 co-crystal[30] but subsequent study has identified an additional 1:1 co-crystal phase.[16] Construction of TPDs in acetonitrile and dichloromethane has allowed for the identification of distinct solution compositions where each individual co-crystal is the thermodynamically stable phase. Knowledge of these solution compositions allows for preparation

of a solution saturated with respect to one specific co-crystal form. This study investigated the behaviour of the 3:2 co-crystal of the TSA/ PH_3PO system when it was placed in a solution saturated with respect to the 1:1 co-crystal, and vice versa. The subsequent solution mediated co-crystal transformation was observed with optical microscopy in real time, and confirmed with PXRD on completion.

The saturation concentrations of TSA and Ph_3PO within the region in acetonitrile solution where the 1:1 and 3:2 co-crystal are respectively stable, were initially measured using a Crystal 16™ system from Avantium Technologies (Figure 1).† For this system, both composition lines for the two co-crystals cross the 1:1 co-crystal solubility, confirming that the 1:1 co-crystal displays congruent dissolution, while the 3:2 displays incongruent dissolution as shown by the previously determined TPD.[16]

The behaviour of each co-crystal in a solution saturated with respect to the other co-crystal respectively was investigated with optical microscopy.§ Seed crystals of the 1:1 and 3:2 co-crystal were produced by heating a 10:20:70 (TSA:Ph_3PO:MeCN) and a 20:10:70 (TSA:Ph_3PO:MeCN) mass fraction solution to 60 °C and cooling at 0.1 °C/min to 20 °C. The resulting solutions were covered with parafilm into which a number of small holes were punched to allow evaporation, and left to stand at room temperature until the crystals increased to a suitable size (3–5 mm). The seed crystals were placed in 5 ml of saturated solution in a temperature controlled optical cell at 20 °C, and a microscope image taken every 15 seconds. The 3:2 co-crystal was placed in a solution containing 0.20 mol·dm^{-3} TSA and 0.15 mol·dm^{-3} Ph_3PO (Figure 1, green x), and the 1:1 co-crystal in a solution containing 0.56 mol·dm^{-3} TSA and 0.08 mol·dm^{-3} Ph_3PO (Figure 1, red x).

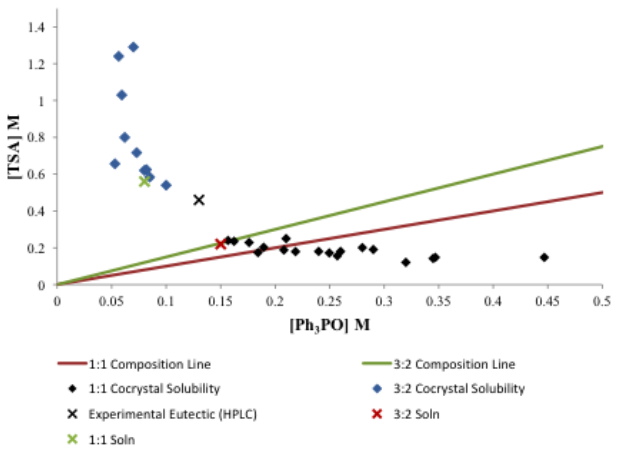

Figure 1: Solubility diagram for TSA/Ph_3PO in acetonitrile. The experimental compositions studied are indicated by the green and red crosses.

The 3:2 crystal undergoes dissolution initially, and additional crystals appear independently of the seed crystal (Figure 2). Growth of the new crystals continued until all the seed phase had dissolved. PXRD of the resulting phase confirmed that the crystals were the 1:1 co-crystal (Figure 4).

During the conversion of the 1:1 crystal, the newly formed crystals cluster closely around the seed crystal and may be associated with the dissolving surface (Figure 3). As each experiment is undertaken without stirring, a local increase in the supersaturation level surrounding the dissolving crystal may occur. This would increase the probability of nucleation and results in the growth of the expected phase in the vicinity of the seed crystal. The final product in this case was confirmed as the 3:2 co-crystal using PXRD.

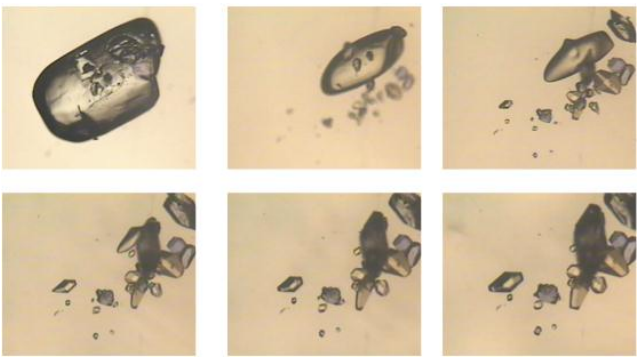

Figure 2: Solution mediated transformation of the 3:2 co-crystal into the 1:1 co-crystal in MeCN. Each image represents a time lapse of 10 minutes. The starting crystal was approximately 4 mm in its longest dimension.

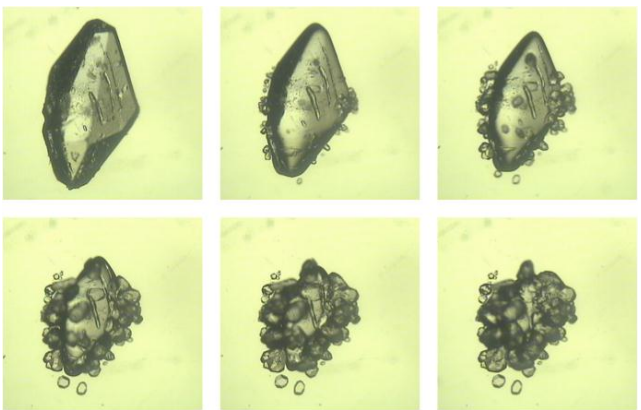

Figure 3: Solution mediated transformation of the 1:1 co-crystal into the 3:2 co-crystal in MeCN. Each image represents a time lapse of 20 minutes. The starting crystal was approximately 4 mm in its longest dimension.

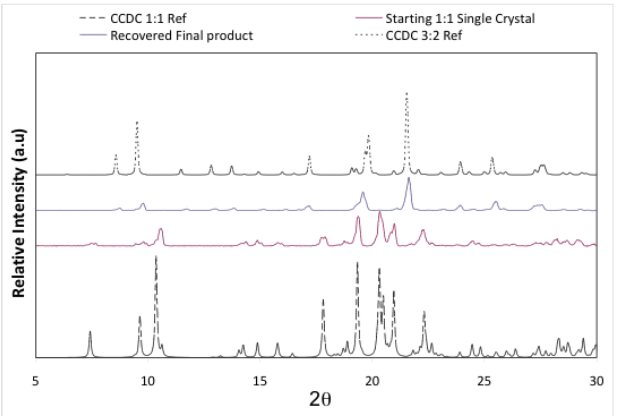

Figure 4. PXRD of 3:2 single crystal which was equilibrated in MeCN saturated with the 1:1 co-crystal and the product of this equilibration. Reference pattern for the two co-crystals are also included.

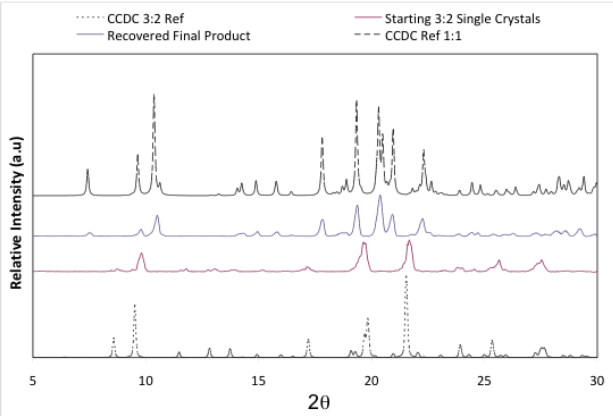

Figure 5. PXRD of 1:1 single crystal which was equilibrated in MeCN saturated with the 3:2 co-crystal and the product of this equilibration. Reference pattern for the two co-crystals are also included.

The recorded images do not clearly define if heterogeneous nucleation occurred on the surface of the co-crystal. As the seed crystals are poorly formed, the habits of the crystals have not been characterised and so identification of the molecular features on each surface preventing such interactions is limited. However, prediction of the morphology by BFDH gives qualitatively similar results to the experimental shapes (Figures 6, 7). From the predicted morphologies, the 1:1 co-crystal is bounded by predominately aromatic functionalities (Figure 6), while the 3:2 co-crystal has an even mixture of aromatic and sulfonamide functional group present on the surfaces (Figure 7). Thus the dominant faces of the two phases lack complementary surfaces and the potential for strong directional interactions to direct a surface to surface interaction as observed in the epitaxially driven polymorphic transformations.[23] Lattice matching calculations using epicalc[31] also indicate that there is no lattice registry between the predicted dominant faces of either phase.

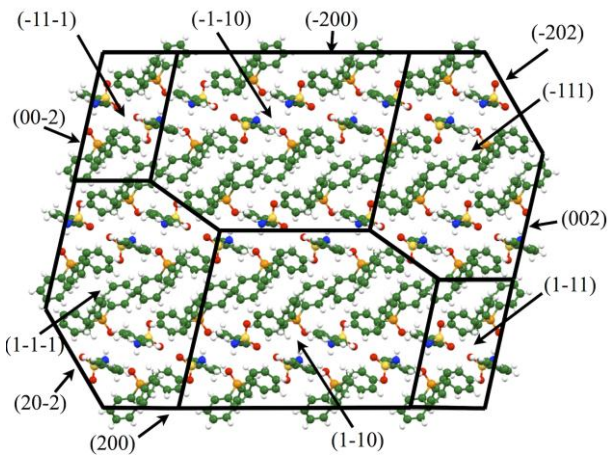

Figure 6. BFDH predicted morphology for the 1:1 co-crystal showing the molecular packing and indexing of selected crystal faces.

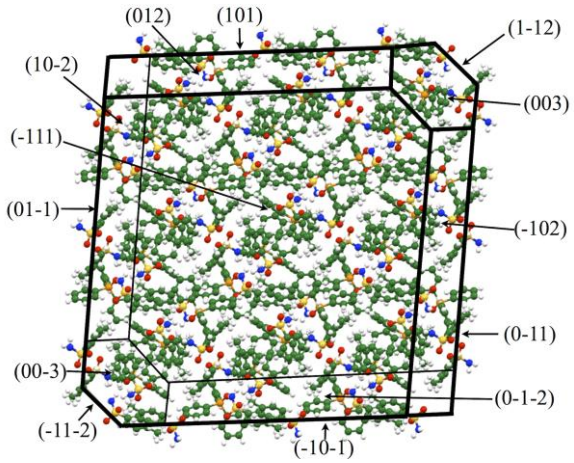

Figure 7. BFDH predicted morphologies for the 3:2 co-crystal showing the molecular packing and indexing of selected crystal faces.

Conclusions

The solution mediated transformation between two co-crystal phases has been demonstrated for the *p*-toulenesulfonamide/triphenylphosphine oxide system in acetonitrile. In this system no surface interaction appears to occur between the dissolving metastable phase and the growing stable phase, unlike many transformations observed for polymorphic systems. This may be due to the differences in surface chemistry of the two phases and suitable epitaxial interactions cannot be formed in this case. This result indicates the importance of understanding co-crystal stability when attempting to isolate a desired co-crystal form.

Notes and references

[a] *Solid State Pharmaceutical Cluster, Materials and Surface Science Institute and the Department of Chemical and Environmental Sciences, University of Limerick, Limerick, Ireland. Fax: +353 61 213529; Tel: +353 61 234166; E-mail: colin.seaton@ul.ie; denise.croker@merck.com*
[b] *School of Chemical Engineering and Analytical Science, University of Manchester, Oxford Road, Manchester, M13 9PL, UK.*
[c] *MSD Ballydine, Kilsheelan, Clonmel, Co. Tipperary, Ireland.*

† Experiments were performed on a 1 ml scale. Mass fractions, on a total mass basis, were selected to represent regions in the TPD where the 3:2 co-crystal or the 1:1 co-crystal are independently stable as indicated in the previously determined ternary phase diagram. The solutions were held at 60 °C for 1 hour to ensure complete dissolution and subsequently cooled at 1 °C/min to 20 °C, and aged for 1 hour. The resulting solids were filtered and analysed with powder X-ray diffraction for phase composition. Reference PXRD patterns for the 3:2 and 1:1 co-crystal were generated from their respective crystallographic information files (CIF) using Mercury 2.4.

§ Optical microscopy was performed using a Zeiss Axioplan 2 polarizing microscope and the Linksys image capture software.

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